



Case Study

You diagnose a patient with Acute Coronary Syndrome and schedule an angioplasty. You explain to the patient that she will need to take clopidogrel, also known as Plavix, for at least 3-6 months to prevent a heart attack. The patient tells you that her father died of a heart attack while taking clopidogrel. So, you decide to look into the pharmacogenetics of clopidogrel response to see if a change in the prescription is indicated.

Learn about optimizing an initial dose, avoiding side effects and the drug therapy recommendations based on genotype in MedGen

Step 1

Look up Clopidogrel response in MedGen

The role of *CYP2C19* clopidogrel metabolism is summarized here. You notice therapeutic recommendations by the FDA and professional societies based on a patient's *CYP2C19* genotype.

Step 2

Go to the NIH Genetic Testing Registry (GTR)

Click on the [See all \(19\)](#) link to go to a list of available genetic tests for clopidogrel response registered in GTR.

Select an appropriate genetic test to order for your patient in the NIH GTR

Step 3

Narrow your search

Check the boxes on the left to filter the list of tests based on your desired parameters. For example: you want the specimen type to be a buccal swab from a lab that is CLIA Certified in the United States.

Step 4

Learn about a specific test

Select a test from the list to see more details: click on [OneOme RightMed comprehensive test](#).

MedGen is a portal to information about human diseases and phenotypes with a genetic component from authoritative sources.

ncbi.nlm.nih.gov/medgen

Definition

Clopidogrel is a thienopyridine antiplatelet agent that prevents platelet aggregation. As a pro-drug, clopidogrel requires hepatic biotransformation to form an active metabolite, which results in reduced platelet inhibition. Amongst other genetic and non-genetic factors, are known to influence variability in clopidogrel metabolism, which results in reduced platelet inhibition. Amongst other genetic and non-genetic factors, are known to influence variability in clopidogrel metabolism, which results in reduced platelet inhibition. Amongst other genetic and non-genetic factors, are known to influence variability in clopidogrel metabolism, which results in reduced platelet inhibition.

Additional description

From Medical Genetics Summaries

Clopidogrel (brand name Plavix) is an antiplatelet agent. Clopidogrel reduces the risk of myocardial infarction (MI) and stroke in patients with acute coronary syndrome (ACS), and in patients with atherosclerotic vascular disease (indicated by a recent MI or stroke, or established peripheral arterial disease). Clopidogrel is also indicated in combination with aspirin in patients undergoing percutaneous coronary interventions (PCI), e.g., the placement of a stent. The effectiveness of clopidogrel depends on its conversion to an active metabolite by CYP2C19. Individuals who carry 2 non-functional copies of the CYP2C19 gene are classified as CYP2C19 poor metabolizers. They have no enzyme activity and cannot activate clopidogrel via the CYP2C19 pathway, which means the drug will have no effect. Approximately 2% of Caucasians, 4% of African Americans, and 14% of Chinese are CYP2C19 poor metabolizers. The 2017 FDA-approved drug label for clopidogrel includes a boxed warning concerning the diminished antiplatelet effect of clopidogrel in CYP2C19 poor metabolizers. The warning states that tests are available to identify patients who are CYP2C19 poor metabolizers, and to consider the use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers. The effectiveness of clopidogrel is also reduced in individuals who are CYP2C19 intermediate metabolizers. These individuals carry one non-functional copy of CYP2C19, with either one normal function copy or one increased function copy. For patients with ACS who are undergoing PCI, the 2013 Clinical Pharmacogenetics Implementation Consortium (CPIIC) guideline for clopidogrel recommends an alternative antiplatelet therapy (e.g., prasugrel, ticagrelor) for CYP2C19 poor or intermediate metabolizers, if there is no contraindication. The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) have also made antiplatelet therapy recommendations based on CYP2C19 genotype. For patients with ACS who receive PCI, they recommend an alternative drug to clopidogrel in poor metabolizers, and for intermediate metabolizers, they recommend choosing an alternative drug, or doubling the dose of clopidogrel to 150 mg daily dose, 600 mg loading dose. <https://www.ncbi.nlm.nih.gov/books/NBK94114>

Professional guidelines

PubMed

Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update.

Scott SA, Sangkuhl K, Stein CM, Hult JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR; Clinical Pharmacogenetics Implementation Consortium. *Clin Pharmacol Ther* 2013 Sep;94(3):317-23. Epub 2013 May 22 doi: 10.1038/clpt.2013.105. PMID: 23698643 Free PMC article

PharmacoScan

RPRD Diagnostics, LLC
United States

OneOme RightMed comprehensive test

OneOme
United States

Rxight Ph

MD I
Un
C
A
Un
CYP2C19
True Health
United States
CYP2C19
Alpha Gen
United States
CYP3A5
Alpha Genomix Laboratories
United States

The NIH Genetic Testing Registry (GTR) is an international database of orderable clinical and research genetic tests and the laboratories that provide them as well as supporting resources about genetic diseases and genes.

ncbi.nlm.nih.gov/gtr

NIH U.S. National Library of Medicine
National Center for Biotechnology Information

Step 5 Browse the test detail page to learn about its clinical and analytical validity, clinical utility and how to order it

Get instructions on how to order this test.

Find names, phone numbers and email addresses of the Lab personnel.

The date this test was last updated is recent. That's good! 🍏

Go directly to the Laboratory's website.

CPT codes are here.

OneOme RightMed comprehensive test
Clinical test ⓘ for [CYP2C19-related poor drug metabolism](#)
Offered by [OneOme](#)

Overview **How To Order** Indication Methodology Performance Characteristics Interpretation Laboratory Contact

Laboratory's Test Page ⓘ
<http://www.oneome.com/rightmed-test>

Test services ⓘ
Clinical Testing/Confirmation of Mutations Identified Previously, **Order code:** RightMed pharmacogenomic test, [comments](#)
pharmacogenetic assay, **Order code:** RightMed pharmacogenomic test, [comments](#)
Result interpretation, **Order code:** RightMed pharmacogenomic test, [comments](#)

How To Order ⓘ
Healthcare providers can order the test directly from OneOme. Orders can be placed electronically (<http://portal.oneome.com/>) or by submitting a requisition form, which is available for download (<http://www2.oneome.com/order-form>). Patients will provide a cheek swab sample, collected on-site or at home using a prescription test kit sent by OneOme. The kit includes simple, step-by-step instructions. After the kit is activated and returned to OneOme in the prepaid packaging, the sample will be processed and test results will be made available through the OneOme portal.
Order URL ⓘ : <http://portal.oneome.com/>

Specimen Source ⓘ
▪ Buccal swab
▪ Isolated DNA
▪ Peripheral (whole) blood
▪ Saliva

Specimen requirements: <http://oneome.com/sample-requirements>

Test Codes ⓘ
CPT® Code(s)†: [81225](#) ⓘ, [81226](#) ⓘ, [81227](#) ⓘ, [81230](#) ⓘ, [81231](#) ⓘ, [81232](#) ⓘ, [81240](#) ⓘ, [81241](#) ⓘ, [81283](#) ⓘ, [81291](#) ⓘ, [81328](#) ⓘ, [81335](#) ⓘ, [81350](#) ⓘ, [81355](#) ⓘ, [81381](#) ⓘ, [81400](#) ⓘ, [81401](#) ⓘ, [81479](#) ⓘ
[Other test codes on lab website](#) ⓘ

Test Order Code ⓘ : RightMed comprehensive test

Reviews ⓘ
PubMed Clinical Queries
Reviews in PubMed

Clinical resources ⓘ
MedGen
OMIM
Clinicaltrials.gov

Practice guidelines ⓘ
CPIC, 2013

Molecular resources ⓘ
OMIM
[View CYP2C19 variations in ClinVar](#) ⓘ
[RefSeqGene](#)
Coriell Institute for Medical Research

Consumer resources ⓘ
Genetic Alliance
MalaCards
MedlinePlus

Step 6 See what information is currently known for this gene's variants in this gene in ClinVar.

Click on [View CYP2C19 variations in ClinVar](#) to see a list of reports of the relationships among variants in the CYP2C19 gene and phenotypes, with supporting data, as provided by submitters like testing laboratories and researchers.

Use ClinVar to help interpret the genetic test result



ClinVar is a database that archives information about human genetic variations and their relationship to human health, with supporting evidence.

ncbi.nlm.nih.gov/clinvar

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ClinVar ClinVar ⓘ 1557[genid] ⓘ
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Home ⓘ About ⓘ Access ⓘ Help ⓘ Submit ⓘ Statistics ⓘ FTP ⓘ

Gene Customize this list... Tabular ⓘ 100 per page ⓘ Sort by Location ⓘ

Clinical significance
Conflicting interpretations (0)
Benign (4)
Likely benign (4)
Uncertain significance (4)
Likely pathogenic (0)
Pathogenic (9)
Risk factor (0)

Search results
Items: 30 ⓘ Total # of variants ⓘ

Review status
Practice guideline (0)
Expert panel (4)
Multiple submitters (0)
Single submitter (8)
At least one star (12)
Conflicting interpretations (0)

Variation Location

| | | |
|----|---|--|
| 1. | GRCh37/hg19 10q11.21-26.3(chr10:42347406-135534747)x1 GRCh37: Chr10:42347406-135534747 | ACADSB, ACTA2, ADRB1, ALOX5, BMPR1A, BNIP3, CHAT, CHUK, A... |
| 2. | GRCh37/hg19 10q23.1-25.1(chr10:85557432-105804295)x1 GRCh37: Chr10:85557432-105804295 | ACTA2, FAS, AR, COL17A1, COX1, CYP2C18, CYP1... |

Allele origin ⓘ

Step 7 Focus on the most significant variants in ClinVar

As you explore the impact of CYP2C19 variants, focus on the most clinically significant, such as those flagged as pathogenic and those that have been reviewed by an expert panel.

The genetic test results arrive! It is reported that the patient is homozygous with two alleles of *CYP2C19* p.Trp212Ter.

Step
8

Search ClinVar with *CYP2C19* p.Trp212Ter

The clinical significance of this variant is that it influences *clopidogrel* response. It has been reviewed by expert panel. Other information is provided here including allele frequency and Other names such as *CYP2C19**3, which is a common clinical nomenclature.

Find actionable information in Medical Genetics Summaries

Step
9

Read more about it in Medical Genetics Summaries.

Learn more about clopidogrel, *CYP2C19* and its role in the drug's metabolism. Go back to the MedGen record for *Clopidogrel* response (ncbi.nlm.nih.gov/medgen/382487). From here, click on the [Medical Genetics Summaries](#) link under **Reviews** on the right sidebar.

Reviews

Medical Genetics Summaries

PubMed Clinical Queries

Reviews in PubMed

NCBI Resources How To

ClinVar

Search ClinVar for gene symbols, HGVS expressions

Advanced

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NEW Click here to see the new Variation Report design! Check out the new layout of these pages!

NM_000769.1(CYP2C19):c.636G>A (p.Trp212Ter)

Variation ID: 16899

Review status: reviewed by expert panel

Awesome!

Interpretation

Clinical significance: drug response

Last evaluated: Jan 12, 2017

Number of submission(s): 4

Condition(s):

- Proguanil, poor metabolism of [MedGen]
- Mephenytoin, poor metabolism of [MedGen]
- clopidogrel response - Efficacy, Toxicity/ADR [MedGen]

See supporting ClinVar records

Allele(s)

NM_000769.1(CYP2C19):c.636G>A (p.Trp212Ter)

Allele ID: 31938

Variant type: single nucleotide variant

Cytogenetic location: 10q23.3

Genomic location:

- Chr10: 94780653 (on Assembly GRCh38)
- Chr10: 96540410 (on Assembly GRCh37)

Other names:

- CYP2C19, TRP212TER (rs4986893)
- CYP2C19m2
- CYP2C19*3

Protein change: W212*

HGVS: NG_008384.2:g.22948G>A



Medical Genetics Summaries is a collection of articles which synthesize pharmacogenetic evidence to provide practical information about genetic testing to guide drug therapy.

ncbi.nlm.nih.gov/books/NBK84114/

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Clopidogrel Therapy and *CYP2C19* Genotype

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NCBI

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Created: March 8, 2012; Last Update: April 18, 2018.

Introduction

Clopidogrel (brand name Plavix) is an antiplatelet agent. Clopidogrel reduces the risk of myocardial infarction (MI) and stroke in patients with acute coronary syndrome (ACS), and in patients with atherosclerotic vascular disease (indicated by a recent MI or stroke, or established peripheral arterial disease) (1). Clopidogrel is also indicated in combination with aspirin in patients undergoing percutaneous coronary interventions (PCI), e.g., the placement of a stent.

The effectiveness of clopidogrel depends on its conversion to an active

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In this Page

Introduction

Drug: Clopidogrel

Gene: CYP2C19

Genetic Testing

Therapeutic Recommendations based on Genotype

Nomenclature of Selected *CYP2C19* Alleles

Acknowledgments

Step
10

Navigate the page to the content of interest

The table of contents enables you to go directly to the *Nomenclature of Selected CYP2C19 Alleles* section.

Step 11 Allele nomenclature standardization

The table Nomenclature of Selected *CYP2C19* Alleles translates the terms used for variants, from the common star allele (*3) to the HGVS expression (NM_000769.1:c.636G>A), and provides links to the *CYP2C19**3 records in dbSNP (rs4986893) and ClinVar (ID 16899).

Nomenclature of Selected *CYP2C19* Alleles

| Common allele name | Alternative names | HGVS reference sequence | | dbSNP reference identifier for location |
|--------------------|---------------------|-------------------------|--|---|
| | | Coding | Protein | |
| <i>CYP2C19</i> *2 | 681G>A Pro227Pro | NM_000769.1:c.681G>A | NP_000760.1:p.Pro227= | rs4244285 |
| <i>CYP2C19</i> *3 | 636G>A Trp212Ter | NM_000769.1:c.636G>A | NP_000760.1:p.Trp212Ter | rs4986893 |
| <i>CYP2C19</i> *17 | -806C>T | NM_000769.1:c.-806C>T | Not applicable - variant occurs in a non-coding region | rs12248560 |

Note: the normal "wild type" allele is *CYP2C19**1 and is reported when no variant is detected.

Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (60).

Table 2.

CPIC (2013) Antiplatelet Therapy Recommendations based on *CYP2C19* Status when considering Clopidogrel for ACS/PCI Patients.

| Phenotype | Examples of diplotypes | Implications for clopidogrel | Therapeutic recommendations for clopidogrel in ACS/PCI ^a |
|--------------------------|--------------------------|--|--|
| Ultrarapid metabolizer | *17/*17 | Increased platelet inhibition; decreased residual platelet aggregation ^b | Dose recommended by drugs label |
| Rapid metabolizer | *1/*17 | | |
| Normal metabolizer | *1/*1 | Normal platelet inhibition; normal residual platelet aggregation | Dose recommended by drug label |
| Intermediate metabolizer | *1/*2 *1/*3 *2/*17 | Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events | Alternative antiplatelet therapy recommended if no contraindication, e.g., prasugrel, ticagrelor |
| Poor metabolizer | *2/*2 *2/*3 *3/*3 | Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events | Alternative antiplatelet therapy recommended if no contraindication, e.g., prasugrel, ticagrelor |

^a The strength of therapeutic recommendations is "moderate" for intermediate metabolizers and "strong" for all other metabolizers. See Supplementary Materials and Methods (Strength of Therapeutic Recommendations) online.

^b The *CYP2C19**17 allele may be associated with increased bleeding risks; see (4).

In this section is a summary of the 2017 Statement from the US Food and Drug Administration (FDA) among others. At the end of the summary, there is a link to [review the complete therapeutic recommendations](#). This takes you to DailyMed where you will find a warning message.

2017 Statement from the US Food and Drug Administration (FDA)

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE *CYP2C19* GENE

The effectiveness of clopidogrel tablets results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally *CYP2C19*. Clopidogrel tablets at recommended doses form an active metabolite and are effective in patients with normal or heterozygous *CYP2C19* alleles. However, patients with two loss-of-function alleles of the *CYP2C19* gene (e.g., *CYP2C19**2/*2, *CYP2C19**2/*3, *CYP2C19**3/*3) may have reduced platelet inhibition and increased risk of adverse cardiovascular events (increase in the risk of bleeding).

Please review the complete therapeutic recommendations that are located here: (1)

Conclusion

The patient's genotype indicates that she is a poor metabolizer for clopidogrel. Based on the available evidence and therapeutic recommendations, you decide to use an alternative antiplatelet drug and change your prescription to prasugrel, which is not metabolized by *CYP2C19*.

Step 12 Clopidogrel dosing recommendations from authoritative sources

All available therapeutic recommendations from medical or professional societies such as CPIC and DPWG are summarized here, with full-text versions cited and linked.

References

MedGen ncbi.nlm.nih.gov/medgen

GTR ncbi.nlm.nih.gov/gtr

ClinVar ncbi.nlm.nih.gov/clinvar

Medical Genetics Summaries ncbi.nlm.nih.gov/books/NBK84114/

Need help? Email us at medgen_help@ncbi.nlm.nih.gov.



Watch a video of this tutorial.
<https://youtu.be/HOixfcWeDxU>



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